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The Public Health Implications of Urogenital Disease

A Focus on Overactive Bladder

PRESENTED BY

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Target Audience

Primary care physicians, nurse practitioners, physician assistants, registered nurses, and other allied healthcare professionals interested in urogenital health.

Statement of Educational Need

Overactive bladder (OAB) is defined as a symptom syndrome suggestive of lower urinary tract dysfunction, and is characterized by urgency and frequency of urination, with or without incontinence. OAB affects over 30 million patients, has significant social consequences, and an estimated economic impact of $26.3 billion per year for patients aged 65 and older with incontinence. Primary care physicians (PCPs) are the first point of contact for most patients with OAB but often are underdiagnosed, undertreated, or referred to a specialist. However, PCPs can effectively treat patients with OAB with a basic understanding of diagnostic methods and currently available therapies.

Acknowledgement

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Accreditation

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for CME (ACCME) through the joint sponsorship of Vanderbilt University School of Medicine and SynerMed Communications. Vanderbilt University School of Medicine is accredited by the Accreditation Council for CME to sponsor continuing medical education for physicians.

Learning Objectives

After reading and reflecting on this monograph, individuals included in the target audience should be able to describe and discuss:

- the significant impact of overactive bladder on public health
- the various types and causes of overactive bladder
- the significant effect of overactive bladder on the quality of life
- considerations in diagnosing the overactive bladder within the primary care setting
- the benefits and disadvantages associated with the various pharmacologic and nonpharmacologic treatment options
- the characteristics of patients who require referral to specialists for assessment and/or management of overactive bladder

Method

This is a CME enduring material. It consists of a monograph and test questions. Please read the monograph, take the test, and submit for CME credit. See page 21.

Term of Approval

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Credit Designation Statement

Vanderbilt University School of Medicine designates this educational activity for a maximum of 2 Category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

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The Public Health Implications of Urogenital Disease: A Focus on Overactive Bladder

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"I welcome you to this important educational program on the identification and management of overactive bladder in the primary care setting.

The issue of urinary incontinence has been important to me since my earliest days in women's health. Almost 10 years ago, I came to appreciate the fact that the critical issue facing women's health was not necessarily how women died—but how they lived. Quality-of-life issues become particularly important in the 7 extra years of life expectancy that women have. And if women are more likely to spend those years disabled, isolated, or with some other condition where their quality of life is less than they had anticipated, it will obviously affect how well and how actively women, and in particular older women, can engage in healthy behaviors.

I hope you will agree that overactive bladder is a tremendous issue for women throughout their lives—it affects their ability to engage in normal physical activity and social engagement, day in and day out.

I also learned early on that urinary incontinence wasn't an issue just of older women, but that overactive bladder also affects men, and that it can begin quite early in life. The clinical information to be presented will be the basis for invaluable educational materials for primary care physicians.

I am proud that the Office on Women's Health has been able to convene this roundtable. I am sure that the educational materials developed from this endeavor will result in a significant difference in the awareness, diagnosis, and management of overactive bladder, particularly in the primary care setting."

Introduction

According to the Standardisation Sub-committee of the International Continence Society (ICS), overactive bladder (OAB) is defined as a "symptom syndrome suggestive of lower urinary tract dysfunction" characterized by "urgency, with or without urge incontinence, usually with frequency and nocturia,"[1] (Table 1) and is characterized by involuntary detrusor muscle contractions during the bladder filling.[2] OAB has significant social and economic ramifications for those patients who are afflicted with this dysfunction, as well as society at large. It is often underdiagnosed and undertreated by clinicians, particularly primary care physicians (PCPs), who often refer these patients to specialists. However, with a basic understanding of etiology, diagnosis, therapeutic options, and expert opinion, PCPs can be empowered to treat OAB patients effectively. In fact, a call for action is necessary for all PCPs to become involved in the medical management of a dysfunction that affects over 30 million patients, particularly when the PCP is very often the first physician that a patient sees when medical problems arise.

Table 1

OAB: Clinical Presentation

Urinary urgency

Strong and sudden desire to void at low bladder volumes

Urinary frequency

>8 micturitions/24 h

Nocturia >2 times per night

Urgency urinary incontinence

Strong and sudden desire to void *plus* involuntary urine loss

Bladder Health Conditions

Serious quality-of-life issue for patients

Characterized by overlapping symptoms

Often undertreated—treatment available

The majority of patients with OAB do not receive treatment or go undiagnosed. Others are undertreated, in which treatment has focused on reducing—but not eliminating—symptoms. Unless specifically addressed by clinicians, most patients are too embarrassed by their symptoms of urinary frequency, urgency, and incontinence to seek medical help. Even patients reporting symptoms of urgency and frequency may still be too embarrassed to mention urinary leakage. Therefore, as part of a detailed history, physicians should always inquire about urinary leakage episodes. As shown in a recent study, physicians were significantly more likely to prescribe treatment medications for patients who reported incontinence versus those who did not report incontinence, 62% versus 46%, respectively (P=0.008).[3] Patients are often unaware that there are effective behavioral and pharmacologic therapies that can significantly reduce and even eliminate their symptoms. Consequently, while patients with severe symptomatology inevitably seek treatment, the majority of patients with mild or moderate symptoms of OAB are often overlooked. This is of particular concern since it has been shown that symptoms of OAB generally progress in severity from urgency and frequency to urinary incontinence.[4] Many patients who are treated may have varying expectations. Some patients will accept moderate improvement and desire maximal tolerability. Other patients, especially those with incontinence episodes, desire total continence.

Communication between patient and physician is essential upon institution of therapy and during continuing treatment.

The medical and psychosocial morbidity associated with OAB is significant (Table 2). Patients with OAB have more outpatient visits and more urinary tract infections (UTIs) than people without OAB.[5] The symptoms of OAB nearly double the risk of being injured in a fall and increase the risk of fall-related, nonspine/nontraumatic bone fractures.[5,6] OAB is a major cause for admittance to long-term care facilities, and it is associated with skin rashes, infections, and pressure sores, as well as depression and sexual dysfunction.[7] Identifying and treating these patients improves their quality of life (QOL), reduces morbidity and mortality, and reduces socioeconomic costs associated with this condition.

According to a 1993 survey reported in the *Morbidity and Mortality Weekly Report* (MMWR), many PCPs feel unprepared to evaluate and/or treat urinary incontinence.[7] The survey further showed that most clinicians do not routinely ask their elderly patients about urinary incontinence, and they are even less likely to routinely elicit bladder health information from their younger patients. Instead, OAB is perceived as a diagnosis necessitating immediate referral to a specialist. However, with a basic understanding of diagnosis and treatment, OAB is usually well within the parameters of a primary care practice. By incorporating a few questions concerning bladder health into a structured intake assessment, clinicians can offer care for the large population of patients with OAB who have unnecessarily been quietly suffering. Because patients

Table 2

OAB-Related Morbidity

General

Increased number of outpatient visits

Increased prevalence of depression

Increased prevalence of sexual dysfunction

Increased number of UTIs

Elderly and/or Institutional Setting

Increased risk of being injured in a fall

Increased risk of fall-related nonspine bone fractures

Major cause for admittance to long-term care facilities

Associated with skin rashes/infections

frequently underreport urinary incontinence, physicians should consider expanding the time frame of their questioning of incontinence symptoms from just the last 24 hours to over the last 4 weeks.[4] This will aid the physician in assessing the magnitude of OAB symptomatology. Current behavioral and medical therapies provide PCPs with the tools to effectively reduce the frequency of micturition and to enable incontinent patients to achieve complete continence, or become dry—with minimal side effects and through simple once-daily and flexible dosing schedules. These therapies allow physicians to meet the treatment expectations of patients, which are consistent with most disease therapies (Table 3). Patients' choices must also be considered, eg, some patients may opt for continence regardless of the side effects, while others may desire a different dosing regimen to ensure fewer side effects with incontinent episodes. When clinicians and their staff forge partnerships with patients and set realistic goals, all will be able to meet their expectations for treatment. Ultimately, successful treatment can minimize morbidity, enhance QOL, reduce depression and sexual dysfunction, and eliminate the self-imposed social isolation so often associated with OAB.

Overview of Overactive Bladder (OAB)

Defining the Terminology

OAB is characterized by urinary urgency, frequency, and incontinence. Urinary frequency generally refers to at least 8 micturitions within a 24-hour period. Urgency is "the complaint of a sudden compelling desire to pass urine which is difficult to defer," and urgency urinary incontinence (UUI) refers to the "complaint of involuntary leakage accompanied by or immediately preceded by urgency."[2]

OAB manifests as detrusor overactivity (DO) with or without DO incontinence. DO can be idiopathic (detrusor instability) or neurogenic (detrusor hyperreflexia) in origin.[10] OAB patients are more likely to present with "OAB dry," or OAB without symptoms of urgency incontinence, than with "OAB wet," (Table 4) in which the symptomatic presentation of frequency and urgency includes UUI and nocturia.[11]

OAB and UUI can coexist with stress urinary incontinence, or involuntary leakage of urine on effort or exertion, or on sneezing or coughing.[2] The etiology and treatment of stress urinary incontinence differ from that of UUI. Approximately 35% (5% to 60%) of patients have stress and/or urgency incontinence symptoms. Having symptoms of both stress and urgency incontinence is often referred to as "mixed incontinence."[11-13]

Table 3

Treatment Expectations

Rapid and effective relief of symptoms*

Minimal side effects*

Simple and flexible dosing schedules†

*Bailey BJ, et al. *Prog Cardiovasc Nurs.* 1997;12(4):23-28.[8]
†Pullar T, et al. *Clin Pharmacol Ther.* 1988;44(5):540-545.[9]

Table 4

Estimated Number of People in the United States With OAB Wet and OAB Dry

	Women			Men		
	In US* (N=17.4M)	In Study† (N=463)	%	In US* (N=15.8M)	In Study† (N=394)	%
OAB Dry	7.9M	209	45.1%	13.2M	329	63.4%
OAB Wet	9.6M	254	54.8%	2.6M	65	36.6%

*Estimate based on 2000 US Census data.
†Stewart WF, et al. *World J Urol*. 2003;20(6):327-336.[11]

Demographics/Epidemiology

Bladder control problems have been referred to as the "last real taboo of the 20th century."[14,15] The World Health Organization (WHO) estimated that urinary incontinence affects nearly 200 million people worldwide, and estimates in the United States range from as low as 13 million persons[15] to as high as 33.3 million persons (Table 4).[11] The great variability reflects the lack of a standardized definition of incontinence, differences in the populations under investigation (especially differences in age and gender), and a focus on the prevalence of incontinence without including the symptoms of urgency and frequency. Unfortunately, studies indicate that less than one in five patients with bladder control problems receive medical assistance or treatment.[16,17] This represents a significant gap between disease sufferers and those who receive treatment.

OAB is common in both women and men, and it is more prevalent in the elderly.[12] The prevalence of urinary

Key Definitions

Overactive bladder: *symptom syndrome suggestive of lower urinary tract dysfunction characterized by urgency, with or without urgency incontinence, usually with frequency and nocturia.*

Urinary urgency: *the complaint of a sudden compelling desire to pass urine that is difficult to defer.*

Urinary frequency: *at least 8 micturitions within a 24-hour period.*

Nocturia: *awakening at night one or more times to void; each void preceded and followed by sleep.*

Mixed incontinence: *urgency urinary incontinence with urinary stress incontinence.*

Urgency urinary incontinence: *the complaint of involuntary leakage accompanied by or immediately preceded by urgency.*

Stress incontinence: *involuntary leakage of urine on effort or exertion, or on sneezing or coughing.*

Detrusor instability: *involuntary detrusor muscle contractions during bladder filling.*

OAB wet: *urinary urgency ± frequency with urinary incontinence.*

OAB dry: *urinary urgency ± frequency without urinary incontinence.*

incontinence also increases after age 40.[18] At least one in three women over age 60 are believed to have experienced urinary incontinence, 14% on a daily basis, compared to only 28% of younger women.[19]

Approximately 33% of women over age 60 are believed to have experienced urinary incontinence (14% on a daily basis) compared to only 28% of younger women.[19]

Two recent surveys—one in Europe[17] and one in the United States[11]—determined that approximately 16% to 17% of the general population has symptoms of OAB, and nearly half (43%) were aged 40 to 64 years.[17] However, men and women present differently: Women are more likely to have OAB with UUI (OAB wet) (55%) and men are more likely to have OAB without UUI (OAB dry) (63%).[11]

Risk Factors

Age, diabetes, a history of recurrent UTIs or childhood enuresis, obesity, restricted mobility, and race have all been identified as risk factors for OAB in women (Table 5). The Heart & Estrogen/Progestin Replacement Study (HERS) Research Group reported an increased risk of urgency incontinence among postmenopausal women with diabetes or frequent UTIs.[20] Pelvic floor disorders, including urinary incontinence, appear to be far more prevalent in women (of all ages) than in men.[13] Approximately 50% of women who seek medical attention for pelvic floor disorders are aged 30 to 60 years.[21] Younger women are more likely to seek attention for genuine stress incontinence, whereas older women are more likely to experience detrusor instability/urgency incontinence.[20,21] Pregnancy, previous vaginal delivery, and postpartum incontinence all appear to be independent risk factors for at least transient UUI.[13,18,22-24] Hysterectomy also appears to increase the subsequent but not immediate risk of urinary incontinence.[18,24,25]

Women are more likely to have OAB with UUI (OAB wet)—55%, and men are more likely to have OAB without UUI (OAB dry)—63%.[11]

Interestingly, there are demonstrated racial differences in urodynamic diagnoses among women with urinary incontinence: African-American women appear to be diagnosed less frequently with genuine stress incontinence and more frequently with detrusor instability than Hispanic, Asian, or Caucasian women.[20,26,27] In addition, there do not appear to be any differences in rates of genuine stress incontinence among Hispanic, Asian, and Caucasian women.

Table 5

Risk Factors for OAB

Age >40	Restricted mobility	Pelvic injury	Childhood enuresis
Recurrent UTIs	Prior vaginal delivery	Childbirth	Obesity
Diabetes	Postpartum incontinence	Hysterectomy	Race

Quality-of-Life Issues

The Constitution of the WHO defines health as a "state of complete, physical, mental and social well-being and not merely the absence of disease or infirmity."[28] As such, QOL issues encompass physical functioning, psychological functioning, social functioning, overall life satisfaction, perception of health status, and pain. While very few QOL assessments focus specifically on OAB, OAB has consistently been shown to have a deleterious effect on health-related QOL.[29] Studies show that both women and men with OAB have a significantly poorer QOL than age- and gender-matched populations.[29] In addition, the inability to control OAB has a greater impact on QOL, particularly social and psychological functioning, than stress incontinence.[30-32] The impact on QOL is associated not only with the severity of UUI[33] but also by the individual's coping abilities.[32] For example, limitations in mobility resulting from OAB appear to be especially distressing to younger women.[31]

The impact on QOL is associated not only with the severity of UUI[33] but also by the individual's coping abilities.[32]

There also appears to be a clear association between urinary incontinence and depression. Women with urinary incontinence have a significantly higher incidence of depression than women without urinary incontinence.[34-37] While depression is frequently a result of chronic medical conditions, including UUI, another hypothesis suggests a common neurochemical pathogenesis associated with reduced central nervous system (CNS) monoamines.[37]

Economic Impact

The economic impact of an illness assesses the total value of all resources used or lost by society as a result of that illness. A recent estimate suggests that the annual direct costs associated with urinary incontinence are more than $16 billion,[38] with 70% of the costs for women attributed to "routine care" (ie, increased laundry, incontinence pads/briefs, nursing care),[39] and total direct and indirect costs have been estimated as $26.3 billion, or $3,565 per individual aged 65 and older with urinary incontinence (Figure 1).[40] This includes the more than $1 billion spent annually on adult disposable products,[41] as well as approximately $1.8 billion spent on costs associated with the medical consequences and complications of OAB (Table 6).[5] The public health cost will significantly increase with the aging of the US population.

Summary

OAB is characterized by urinary urgency, frequency, and incontinence. Suspicion of OAB should not be limited to the elderly—women and men of all ages are potentially at risk. Patients are more likely to seek treatment if they experience incontinence. Conversely, patients who report symptoms of urgency and frequency may not disclose these episodes due to embarrassment. The majority of patients who report symptoms of OAB either do not receive treatment or go undiagnosed. Others are undertreated in which treatment has focused on reducing but not eliminating symptoms.

Table 6

Consequences of OAB

Treatment for falls/fractures

Treatment for skin infections

Treatment for UTIs

Psychosocial consequences

Nursing home admissions

Lengthened hospital stays

Risk factors associated with OAB for women include not only age, but diabetes, a history of recurrent UTIs or childhood enuresis, obesity, restricted mobility, and race. It is essential for clinicians to equally assess both the degree of symptomatology as well as the effect of OAB on the patient's QOL. Many patients have developed coping strategies to accommodate their symptoms and may be unaware of the availability of effective therapeutic approaches that will enable them to resume a higher-level QOL. OAB impacts not only patients' QOL, but the economy as well, with public health costs significantly increasing as the US population ages. With appropriate use of currently available therapies, PCPs can effectively treat OAB, with the goal of achieving complete continence in patients with UUI.

Etiology and Pathophysiology of OAB

Anatomy and Physiology of Normal Urinary Function

Normal lower urinary tract function can be divided into the storage and emptying functions of the bladder (detrusor) (Table 7) and the bladder outlet (sphincter) under neurologic control. During urinary storage the bladder accommodates urine at a low intravesical pressure while the outlet remains competent so that there is no leakage. During urinary emptying, the bladder contracts in a coordinated fashion while the outlet relaxes so that there is no obstruction.

Table 7

Requirements for Urinary Storage and Emptying

Urinary Storage

Low pressure compliant bladder/reservoir

Absence of uninhibited contractions

Competent bladder outlet

Bladder Emptying

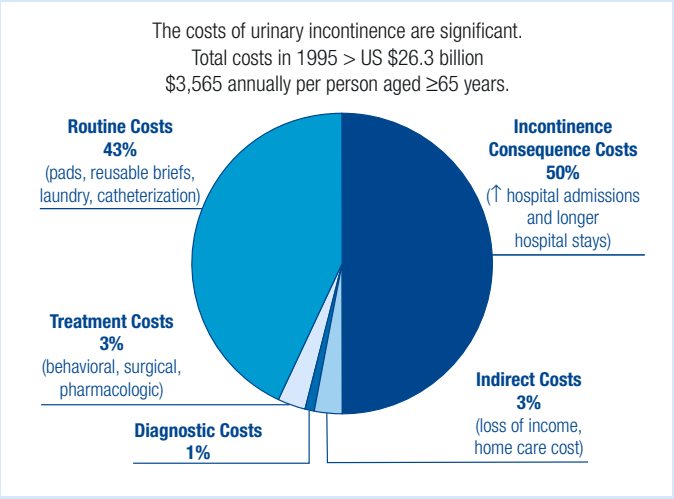
Sustained bladder contraction

Coordinated lowering of outlet resistance

COORDINATION OF STORAGE AND EMPTYING UNDER CENTRAL NERVOUS SYSTEM CONTROL

Figure 1

The Costs of Urinary Incontinence



Wagner TH, Hu TW. *Urology*. 1998;51(3):355-361.[40]
Hampel C, et al. *Urology*. 1997;50(6A suppl):4-14; discussion 15-17.[42]

OAB may be associated with involuntary bladder contractions. Involuntary bladder contractions that overcome the outlet resistance are incontinence episodes. These functions of the bladder and outlet are under neurologic control.

The primary neurotransmitter associated with bladder contractility is acetylcholine. The efferent autonomic parasympathetic fibers of the pelvic nerve stimulate bladder smooth muscle. Afferent impulses from the bladder, sphincter, and pelvic floor and the efferent output are mediated in the sacral cord as well as in the pontine micturition center. The pontine micturition center provides bladder and sphincter coordination. Voluntary control is maintained in the cerebral cortex. Alteration of the central inhibitory pathways to the pontine or sacral areas, secondary to intracranial or spinal cord disease, may result in neurogenic bladder dysfunction. More subtle dysfunctions of the afferent and efferent systems result in bladder instability and OAB symptoms.

Bladder function abnormalities should be classified as a failure of urinary storage or a failure of urinary emptying. OAB is a disorder of urinary storage.

Clinical Pathophysiology of OAB in Women

Many factors can interfere with the ability of the urinary bladder to function normally in a woman—including variations in the urethral wall and fibromuscular underpinnings,[43,44] childbirth, obstetric and surgical procedures/complications,[45] the aging process/menopause, obesity, and neurologic problems. [The pathophysiology of OAB in men and children is discussed later in this publication.]

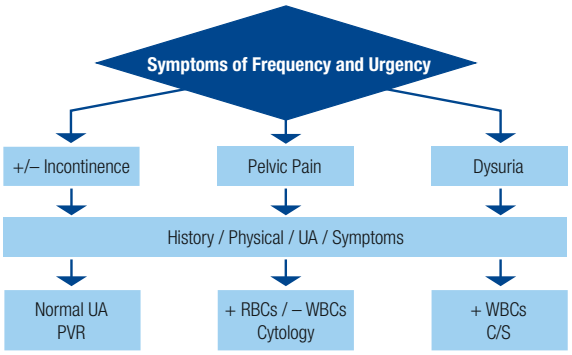
Diagnosis of OAB

Diagnostic Process

The diagnosis of OAB is certainly within the purview of a PCP for the majority of patients. However, while some patients schedule an office visit specifically to address bladder symptoms, the clinician also can raise the possibility of bladder health concerns through brief but targeted questioning during annual examinations. Because many bladder health concerns are characterized by urinary frequency and urgency, the clinician must first isolate additional symptomatology that might be suggestive of a specific bladder health syndrome (eg, urgency incontinence for OAB or pelvic pain for interstitial cystitis [IC]) (Figure 2). Clinicians can utilize common diagnostic tools, including a patient history and physical examination, and a symptomatic assessment to achieve a diagnosis of OAB.

Figure 2

Diagnostic Algorithm



C/S=culture and sensitivity; PVR=postvoiding residual cystometry; UA=urinalysis.

Roger R. Dmochowski, MD, FACS.

History and General Medical Assessment

A patient history and general medical assessment should delineate the nature and duration of genitourinary symptoms and identify the possible etiology of the bladder symptoms, including bladder, neurologic, or pharmacologic causes. To this end, the clinician elicits information regarding any prior surgeries, particularly those that might affect the genito-urinary tract, the patient's current disease and mental status, and any impediments to mobility. Contributing comorbidities and concomitant medications that might be causative factors for the symptoms should be identified. It should be noted, however, that a patient's medical history is not sufficient as the sole diagnostic determination of either UUI stress incontinence or OAB.[46]

Many neurologic conditions can cause OAB symptoms. Women with multiple sclerosis (MS) will often initially present or have as a primary presenting complaint urinary urgency, frequency, or urgency incontinence with or without retention. In addition, it is estimated that at least 80% of people with MS will experience symptoms of urinary dysfunction.[47,48] Urgency incontinence and OAB also have been shown in up to 90% of patients with Parkinson's disease.[49] In addition, OAB can result from intravesical causes, bladder instability secondary to obstruction, or from specific medications.

The clinician also can raise the possibility of bladder health concerns through brief but targeted questioning during annual examinations.

Symptomatic Evaluation

An integral component of the diagnostic process is an evaluation of the symptomatic presentation, focusing on frequency of incontinence, perceived quantity of leakage, and perceived impact of leakage (and symptoms) on everyday life (Table 8). A bladder diary and/or pad test (in which the patient reports how many [and what kind of] pads are used on a daily basis) may be helpful in the diagnosis as well as during the management phase to assess symptomatic improvement. Currently, there are more than 150 QOL assessments for this disease process, with no standardization. Experts at *this* conference recommend a visual analog scale for assessing how "bothered" the patient is by the symptoms (Figure 3). PCPs also should ask patients to identify the most bothersome symptom.

Table 8

Diagnosing OAB in Women: Symptomatic Appraisal

Quantification	Qualification and Bother
Degree of urgency	Incontinence episodes
Frequency of episodes	Perceived quantity of leakage
Nocturia	Perceived impact of leakage on activities of daily living

Physical Examination

The physical assessment should include an abdominal examination after voiding to detect a palpable bladder, a genitourinary examination to assess perineal sensation and skin condition of the external genitalia, a rectal examination to assess anal tone and pelvic floor function, and a vaginal examination to assess prolapse, pelvic floor function and strength, and estrogen status (Table 9). Patients with suspected stress urinary incontinence should undergo a stress test, which quantifies urinary leakage immediately upon increases in intra-abdominal pressure.

Figure 3

Visual Analog Scale

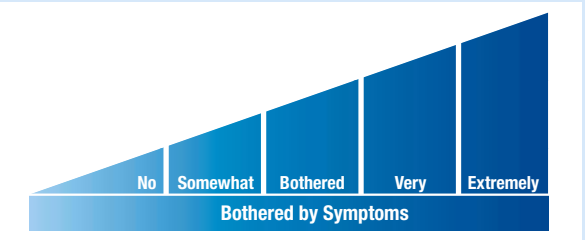


Table 9

Diagnosing OAB in Women: Physical Examination/Laboratory Assessment

Physical Examination

Assessment	Evaluating:
Postvoid abdominal exam	palpable bladder
Perineal exam	sensation
Rectal exam	anal tone, pelvic floor function
External genitalia	skin condition
Vaginal exam	pelvic floor function and strength, estrogen status
Stress test for urinary incontinence	stress incontinence

Laboratory Assessment

Urinalysis

Initial Laboratory Testing

The initial clinical assessment includes a urinalysis (with or without culture) to rule out UTI.

Advanced Analyses

More advanced techniques include a urodynamic evaluation to objectively assess storage and emptying function and cystoscopy to rule out intravesical causes. Postvoiding residual cystometry (PVR) is indicated for the clinical suspicion of decreased bladder emptying. Table 10 lists complicating factors that suggest the need for referral to a specialist. A knowledgeable PCP can safely assume responsibility for the follow-up and ongoing management of most of these patients.

Differential Diagnosis of OAB

OAB, one of several bladder health syndromes, including IC (which will be discussed later in this monograph), is characterized by overlapping symptoms, including urinary urgency and urinary frequency, with or without urgency incontinence and with or without pain, in the absence of bacterial etiology or other lower urinary tract pathology (Figure 4). In contrast, UTIs have similar symptomatology but with a bacterial etiology. Outlet obstruction and urinary retention may indicate a more serious underlying genitourinary pathology.

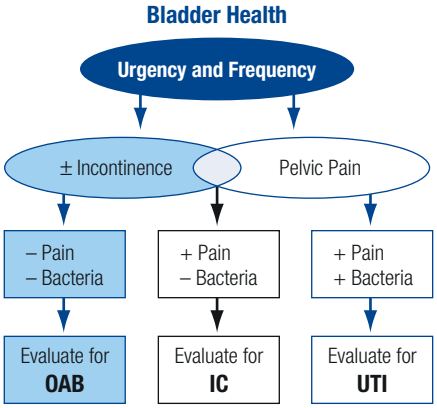
Table 10

Indications for Specialty Referral

Hematuria
Urinary retention or incomplete emptying
Recurrent UTIs
Prostatic obstruction
Recent pelvic surgery
Neurogenic bladder
Unclear diagnosis
Treatment failure

Figure 4

Schematic for Managing Bladder Health Conditions



OAB is a symptom complex, not a specific disease; as such, there are numerous conditions with similar symptomatology. An important step is to determine whether the concern is in the bladder or the bladder outlet, and whether the patient is having a problem with failure to store or to empty urine (Figure 5). OAB and urgency incontinence involve problems in failing to store urine in the bladder, whereas stress incontinence is a bladder outlet-associated problem of failure to store urine. Discussion regarding stress incontinence and disorders associated with a failure to empty urine (including urinary retention or urinary obstruction) is outside the scope of this publication. Diseases or conditions to consider in the differential diagnosis can be found in Table 11, page 7. The effects of concomitant medication classes on the bladder and outlet, another factor to consider, are listed in Table 12, page 7.

Figure 5

Classification: Storage and Emptying Disorders

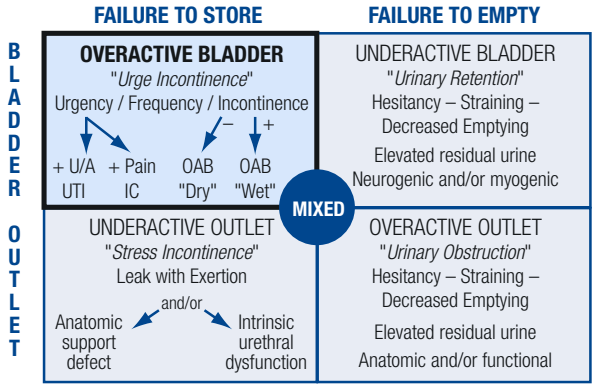


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Table 11

OAB: Differential Diagnosis

Effects on Input/Output
Diabetes mellitus
Diabetes insipidus
Diuretic usage

Effect on LUT Function
Fecal impaction
Obstruction
Neurologic diseases
Psychogenic medications

Bladder Infection/ Inflammation
Urinary tract infection
Interstitial cystitis
Radiation cystitis
Atrophic vaginitis
Bladder neoplasia
Urolithiasis
Diverticulum
Bladder irritants
Vulvodynia/vestibulitis
Vulvovaginitis

Ability to Toilet
Psychosocial causes
Mobility
Dexterity
Mental status

Table 12

Commonly Observed Effect of Concomitant Medication Classes on Bladder and Outlet

Medications which decrease bladder contractility:	anticholinergics/smooth muscle relaxants
Medications which increase bladder contractility:	cholinergics
Medications which increase outlet resistance:	α-agonists
Medications which decrease outlet resistance:	α-blockers

Differential Diagnosis

Intake/output – polydipsia and/or polyuria

Inflammation/infection

Urinary retention/overflow

Obstruction/overflow

Stress incontinence

Mobility/dexterity/mental status

The complex of OAB symptoms including urgency and frequency, with or without incontinence, are further subdivided into "OAB wet" (urgency and frequency with incontinence) and "OAB dry" (urgency and frequency without incontinence) (Tables 13 and 14). "OAB with pain" encompasses those chronic pelvic pain syndromes (CPPSs) (discussed later in this publication) that present with urgency, frequency, suprapubic pain or pressure, vaginal burning, dysuria, and/or dyspareunia (Table 15). Finally, patients who have a positive urine culture with symptoms of urgency and frequency are diagnosed with UTI and treated with appropriate antibiotics.

Bladder Health Questionnaire

The Bladder Health Questionnaire (BHQ) was designed by the roundtable meeting participants as a symptom appraisal instrument that can be used by the practitioner for any level of interaction or analysis of the patient with voiding dysfunction. The goal of the BHQ was utility, yet it provides expanded appraisals to address patients at several levels of severity of symptoms for use in continued follow-up evaluations.

As previously discussed, the use of an assessment tool that can succinctly and adequately capture the patient's specific symptoms is very useful for initial and subsequent evaluation and management in this QOL-disrupting group of symptoms. Any instrument that is used should be easy for patient and practitioner alike, encompass the patient's observations, and be malleable to different situations and practice styles.

The enclosed BHQ addresses these needs in a quantitative and longitudinal fashion (Table 16). For those practitioners interested in initial determination and assessment with the potential for either directed initial therapy or triage to

Table 13

Differential Diagnosis (Bladder): OAB Wet (Urgency ± Frequency + Incontinence)

Detrusor instability

Detrusor hyperreflexia
- Multiple sclerosis
- Parkinson's disease
- CNS: infarct/neoplasia/infection
- Spinal lesion: infarct/neoplasia/injury

Low compliance bladder
- Radiation
- Infection

Table 14

Differential Diagnosis (Bladder): OAB Dry (Urgency ± Frequency – Incontinence)

Bladder irritants
Diabetes mellitus
Diabetes insipidus
Psychogenic medications
Psychosocial causes
Diuretics
Fecal impaction
Benign prostatic hyperplasia

Table 15

Differential Diagnosis: OAB Pain

Interstitial cystitis
Urinary tract infection
Vestibulitis/vulvodynia
Urethral diverticulum
Atrophic vaginitis
Vulvovaginitis
Urolithiasis

Table 16

Bladder Health Questionnaire

Initial Screening Questions

1. When you have the urge to urinate, do you leak before reaching the restroom? ❑ Yes ❑ No
2. Do you leak urine when you cough, sneeze, bend, or do activity? ❑ Yes ❑ No
3. When you finish urinating, does your bladder feel empty? ❑ Yes ❑ No
4. Is your frequent urination (urgency/nocturia) a bother to you? ❑ Yes ❑ No
5. Is your urine leakage a bother to you? ❑ Yes ❑ No

Detailed Screening Questions to Assess Severity of Symptoms

1. On average, how many pads do you use each day? ❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8 ❑ More than 8
2. On average, are the pads: ❑ Damp ❑ Moderately wet ❑ Soaked
3. When you need to urinate, is it associated with urgency? ❑ Yes ❑ No
4. On average, how often do you urinate during the day? ❑ 20-60 min ❑ 1 hour ❑ 2 hours ❑ 3 hours ❑ 4 hours ❑ >4 hours ❑ Variable
5. On average, how many times do you get up from sleeping to urinate? ❑ 2 ❑ 2-3 ❑ 3 ❑ 3-4 ❑ 4 ❑ 4-5 ❑ 5 ❑ 5-6 ❑ 6 ❑ More than 6
6. Is your urine leakage a bother to you? ❑ Yes ❑ No
7. On average, is your urine flow: ❑ Good ❑ Poor ❑ Reasonable
8. When you urinate, do you strain or push? ❑ Yes ❑ No
9. Do you drink a number of caffeinated or carbonated drinks daily? ❑ Yes ❑ No

Follow-up Questionnaire to Assess Progress of Therapy

1. To what degree has your urine leakage problem improved? ❑ Worse ❑ 0% ❑ 10% ❑ 20% ❑ 30% ❑ 40% ❑ 50% ❑ 60% ❑ 70% ❑ 80% ❑ 90% ❑ 100%
2. On average, how many pads/day do you use? ❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8 ❑ More than 8
3. On average, are the pads: ❑ Damp ❑ Moderately wet ❑ Soaked
4. To what degree has your frequent urination improved? ❑ Worse ❑ 0% ❑ 10% ❑ 20% ❑ 30% ❑ 40% ❑ 50% ❑ 60% ❑ 70% ❑ 80% ❑ 90% ❑ 100%
5. Is your flow: ❑ Improved ❑ Not improved
6. Side effects: ❑ Mild ❑ Moderate ❑ Severe ❑ Reason to discontinue
7. Describe the level of satisfaction with your treatment: ❑ Satisfied ❑ Partially satisfied ❑ Not satisfied
8. Would you desire a higher dosage of medication to further improve your symptoms? ❑ Yes ❑ No
9. Would you desire a lower dosage of medication to decrease any side effect? ❑ Yes ❑ No
10. Refer: ❑ Uncertain diagnosis ❑ Hematuria ❑ Other complicating factors ❑ Unsuccessful therapy

specialist, the first five questions provide a brief estimate of the patient's urgency, frequency, and/or stress symptomatology and the overall level of bother that the patient experiences from these symptoms. This allows, when combined with subsequent exclusionary factors from the history and physical, the potential targeted use of behavioral, dietary, and/or pharmacologic therapy for properly selected patients. The first group of questions also permits a more defined referral process for PCPs.

The second group of queries provides a more substantive appraisal of symptomatic severity and associated factors possibly contributory to the patient's voiding dysfunction. The initial subgroup of questions addresses the three components of the OAB complex and assesses incontinence severity by amount and magnitude (captured by pad use and pad soilage), as well as the degree of urinary frequency as exact daytime and nighttime increments (so as to provide baseline data for stratification against later treatment response). The degree of urinary urgency also is initially appraised (this being the least easy of the symptoms to assess due to the lack of an objective correlate). Next, an estimate of bladder emptying occurs, as this subgroup of complaints is very important to certain patient populations (the postmenopausal woman and the elderly). These are factors that may complicate pharmacologic intervention and indicate a patient at risk for worsening bladder emptying after the initiation of anticholinergic drugs. Lastly, the final question addresses the recognition of volume of fluid intake and ingested agents that may exacerbate OAB symptoms.

The last group of questions provides useful postintervention assessment of a patient's symptomatic response to treatment. The patient's response to treatment is evaluated based on the percentage of change in symptom burden, magnitude of impact on incontinence (change in pad use and number of incontinence episodes), and improvement in frequency. Next, bladder emptying is assessed by a follow-up to concerns raised by the prior set of questions. A measurement of the tolerability of the intervention also is made by the patient's identification and estimation of any potential treatment-related side effects. Finally, the patient provides feedback regarding his/her overall improvement and whether a change in dosage would create a more desirable effect on symptoms and side effects. The final item on the BHQ provides the practitioner with reasons for referral or guidance with those patients who have not had a satisfactory response to intervention.

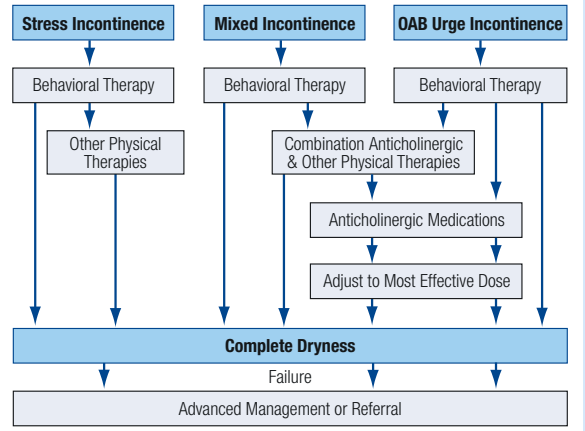
The BHQ is a simple, rapid, yet inclusive instrument that addresses the various OAB complaints and provides the interested practitioner with a structured approach to therapy promulgation and assessment.

Therapeutic Options

The goal of treatment for OAB is to eliminate the symptoms of urinary frequency, urgency, and urgency incontinence. OAB is not an acute illness, and therapy should utilize a chronic illness model to allow for ongoing management and follow-up. As with most medical concerns, management of OAB should proceed from the least invasive to the most invasive strategy (Figure 6). A combination of behavioral therapy with pharmacologic management often affords patients a greater benefit than the use of either therapy alone. Of critical importance is establishing realistic treatment goals with the patient. Although patients may be content just reducing the symptoms, some of the available therapies can help them work towards and/or attain complete continence.

Figure 6

Treatment of Urinary Incontinence in the Primary Care Setting



Of critical importance is establishing realistic treatment goals with the patient.

Nonpharmacologic Options

Behavioral Interventions

Numerous behavioral interventions can significantly reduce the symptoms of OAB, particularly urgency incontinence; however, none is considered to be curative. In general, nonpharmacologic options include behavioral treatment that involve either bladder training, which focuses on voiding habits and bladder function and/or pelvic floor muscle training, which emphasizes modifying the bladder outlet and increasing sphincter resistance (Table 17). The current approach is to individualize a program using a variety of these nonpharmacologic treatments, in conjunction with home practice and exercise, voiding schedules, "urgency" strategies, bladder diaries, and fluid and diet management.

Table 17

Nonpharmacologic Therapies

Bladder drill: inpatient bladder retraining
Bladder training: emphasis on voiding habits and bladder function
Timed voiding with increasing intervals between voids
Urgency-control strategies
Pelvic floor muscle training: modifying the bladder outlet and increasing sphincter resistance
Biofeedback
Verbal feedback

Research indicates that the greatest beneficial results occur with a combination of nonpharmacologic and pharmacologic therapies.

The earliest behavioral intervention was bladder drill, an intensive program often conducted on an inpatient basis to help the patient increase the interval between voids and normalize bladder function to reach dryness. Bladder training is a more gradual, outpatient modification of bladder drill with similar goals: to reduce the frequency of urination, increase bladder capacity, and normalize bladder function. Bladder training involves developing a voiding schedule and then gradually increasing the intervals between voids, thereby modifying bladder function. It is primarily useful for urgency incontinence but has been shown to be successful in the management of stress incontinence. Patients also are taught to use coping strategies, including distraction and relaxation.[50]

Clinical Trials on Behavioral Interventions

Bladder training has been shown to be effective in managing the symptoms of OAB. A randomized clinical trial examined the efficacy of bladder training in 123 postmenopausal women (≥55 years) urodynamically diagnosed with either urethral sphincteric incompetence (stress incontinence) (n=88) or detrusor instability with or without concomitant sphincteric incompetence (urgency incontinence) (n=35). Bladder training reduced the number of incontinent episodes by 57% for both groups, and the quantity of fluid loss was reduced by 54%. Women with detrusor instability had greater reductions in fluid loss than women with stress incontinence.[52]

In another randomized, placebo-controlled trial, 197 community-dwelling women aged 55 to 92 years with urodynamically demonstrated urgency incontinence or mixed incontinence were randomized to receive either 4 sessions of biofeedback-assisted behavior treatment (pelvic muscle training and exercise), drug treatment with immediate-release oxybutynin, or placebo.[53] Behavioral treatment led to a mean 80.7% reduction of incontinent episodes and was significantly more effective than drug treatment (mean 68.5% reduction, P=0.04), and both were significantly more effective than the placebo control condition (mean 39.4% reduction, P<0.001 and P=0.009, respectively). In addition, for all parameters, patients perceived the greatest improvement and satisfaction with the behavioral intervention. Patients in the drug group had a significant increase in bladder capacity (P<0.001), while patients in the behavioral program had only a minimal increase.

A follow-up conditional crossover trial examined the effects of combining behavioral treatment with drug treatment for urgency incontinence.[54] Women received either 4 sessions (over 8 weeks) of biofeedback-assisted behavioral training followed by 8 weeks of behavioral training combined with drug therapy (oxybutynin) or 8 weeks of drug therapy followed by the combination of drug therapy with behavioral training. In both arms of the trial, the combination of behavioral training plus drug therapy further increased the mean reduction of incontinence, suggesting an additive effect.

A recent trial examined the specific role and benefit of biofeedback in the treatment of urgency incontinence in older women.[51] Two hundred twenty-two women, aged 55 to 92 years, were randomly assigned to receive either 8 weeks (4 sessions) of biofeedback-assisted behavioral training, 8 weeks (4 visits) of behavioral training without biofeedback (verbal feedback based on vaginal palpation), or 8 weeks of self-administered behavioral training using a self-help booklet (control condition). Among the three treatment arms, verbal feedback without biofeedback led to the greatest mean reductions in incontinence and was associated with the highest level of patient satisfaction; however, all three programs led to comparable improvements in urgency incontinence.

Research indicates that the greatest beneficial results occur with a combination of nonpharmacologic and pharmacologic therapies.

In comparison, behavioral training, including biofeedback, verbal feedback, and physical therapy/pelvic floor muscle training or rehabilitation, focuses less on altering voiding frequency and more on altering the physiologic responses of the bladder and pelvic floor muscles. This goal is attained through modification of the bladder outlet using pelvic floor muscle training and exercise. Traditionally, behavioral training was used for stress incontinence but has recently been shown effective for urgency incontinence, including occlusion of bladder outlet and inhibition of detrusor contraction.[51]

In general, behavioral treatments are safe and effective options that can reduce urgency incontinence, at least in community-dwelling, motivated persons. They are not associated with side effects, but they do require a significant commitment in additional provider time and support for patient education. Unfortunately, nonpharmacologic/behavioral treatments are underutilized, often because they are misperceived as ineffective or too intensive. In addition, the high rates of success reported in clinical trials may be, in part, a reflection of the intensive training and follow-up provided during the study, and they may not necessarily translate into similarly high success rates in a typical clinical practice. While behavioral programs are not curative, results can be maximized when combined with pharmacologic therapies.

Pharmacologic Options

Commonly Used Medications

Oxybutynin immediate-release (oral: 5 mg, 10 mg, 15 mg)

Oxybutynin extended-release (oral: 5 mg, 10 mg, 15 mg)

Tolterodine immediate-release (oral: 1 mg, 2 mg)

Tolterodine extended-release (oral: 2 mg, 4 mg)

The bladder is a smooth muscle containing muscarinic receptors (particularly M2 and M3) that are responsible for detrusor muscle contractions; as a result, pharmacology has focused on the use of anticholinergic/antimuscarinic agents. The goal of pharmacologic therapy is to reduce the frequency of micturition and incontinent episodes—and ideally to enable the patient to achieve complete continence. The two most commonly used anticholinergics/antimuscarinics are oxybutynin and tolterodine tartrate. Additional medications include the antispasmodic dicyclomine HCl, the antimuscarinics propantheline and hyoscyamine, the antispasmodic flavoxate, and the tricyclic antidepressant imipramine, which has mild anticholinergic and mild sympathetic effects (Table 18). Imipramine, which is not indicated but sometimes used, has been shown to increase urethral tone while decreasing bladder tone, but the Agency for Health Care Policy and Research (AHCPR) guidelines recommend its use only in "carefully evaluated patients."[55]

Table 18

Pharmacologic Therapies

Combined Anticholinergics/Antispasmodics	
Oxybutynin	Extended-release (oral: 5-30 mg qd) Immediate-release (oral: 2.5-5 mg bid-qid) Extended-release transdermal (1.3-3.9 mg q3d)
Dicyclomine	Immediate-release (oral: 10-20 mg tid-qid)
Antimuscarinics	
Tolterodine	Extended-release (oral: 2-4 mg qd) Immediate-release (oral: 1-2 mg bid)
Propantheline	Immediate-release (oral: 7.5-15 mg qid)
Hyoscyamine	Oral and sublingual (oral: 0.125 mg qid)
Antispasmodic	
Flavoxate	Immediate-release (oral: 100-200 mg qid)
Tricyclic Antidepressant	
Imipramine	Immediate-release (oral: 10-25 mg tid)

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Anticholinergic/Antimuscarinic Agents

Anticholinergic/antimuscarinic agents remain the standard of care, and they are recommended in the AHCPR guidelines as first-line pharmacologic therapy for patients with detrusor instability.[41] Medication should begin with a single agent at the lower or intermediate recommended dose, with gradual increases until the desired effect (continence) is achieved or until adverse effects become intolerable.

As a drug category, anticholinergic/antimuscarinic agents have been shown to be effective in reducing the symptoms of OAB; however, they are associated with significant dry mouth, resulting in a high rate of treatment discontinuation. Other effects associated with anticholinergic agents include blurred vision and constipation. The two most frequently prescribed anticholinergic/antimuscarinic agents for the management of OAB in the United States are oxybutynin and tolterodine. The clinical trials for these agents are summarized on pages 13 and 14.

Oxybutynin

Oxybutynin is an anticholinergic agent with direct musculotropic (antispasmodic) effects (Table 19). It has mild calcium channel blockade properties and is a strong local anesthetic. Oxybutynin has been used by nearly 4 million patients during the past three decades, and it has been considered the gold standard for the treatment of OAB for the past 25 years.

The original formulation of oxybutynin was an immediate-release (OXY-IR) oral tablet dosed at 5 mg one to four times per day to a maximum dose of 20 mg/d. Studies have demonstrated that OXY-IR results in a mean decrease in incontinence of 52% and a mean 24-hour reduction in frequency of micturition of 33%.[56] Unfortunately, the high overall subjective improvement rate (74%) associated with OXY-IR was offset by the high mean percent of patients reporting side effects (70%)[56]: between 60% and 80% of patients experience dry mouth, resulting in a significant level of discontinuation.[57] In some patients, the adverse-effect profile can be reduced by adjusting the dose down to 2.5 mg bid.

Table 19

Oxybutynin: Overview

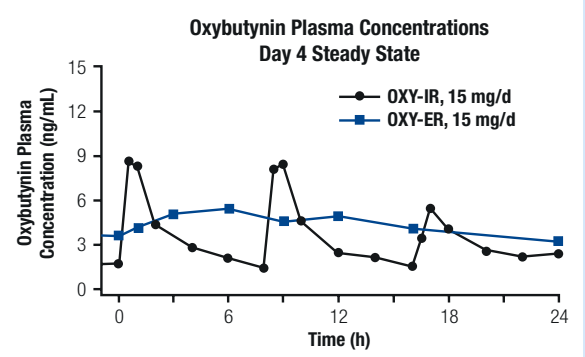
- Anticholinergic/antispasmodic
- Mild calcium channel blockade
- Strong local anesthetic
- Gold standard for treatment of OAB for nearly 3 decades
- Two oral formulations
  - Immediate-release (OXY-IR)
    - High level of efficacy
    - Dosed 5 mg 1-4 times/d
    - High incidence of dry mouth
  - Extended-release (OXY-ER)
    - Once-daily dosing: 5 mg, 10 mg, 15 mg
    - Improved efficacy and tolerability versus OXY-IR
    - Allows for higher dosing for achievement of treatment goals

In 1999, the approval and introduction of a once-daily, extended-release formulation of oxybutynin—OXY-ER (Ditropan XL®, Ortho-McNeil Pharmaceutical, Inc, Raritan, NJ)—provided an alternative that had comparable efficacy to the immediate-release formulation and an improved tolerability profile. By utilizing osmotic release technology (OROS®), the active agent (oxybutynin) is released within 3 hours of administration (Figure 7). Pharmacokinetic studies demonstrate that the controlled-release oxybutynin system results in a gradual increase in mean plasma concentration over approximately 6 hours following dosing and remains fairly constant over 24 hours; in contrast, OXY-IR formulations cause a rapid rise in mean plasma concentrations within the first hour after dosing, which then declines (Table 20).[58] The controlled-release formulation affords a much lower mean degree of fluctuation than the immediate-release formulation and provides a higher mean relative bioavailability (153% versus 69% for OXY-IR), possibly due to reduced first-pass metabolism.[58] The even

Figure 7

Oxybutynin Pharmacokinetics

OXY-ER Minimizes Peaks and Troughs Associated With Oxybutynin



Gupta SK and Sathyan G, *J Clin Pharmacol*. Volume 39 Issue 3, pp 289-296, ©1999 by American College of Clinical Pharmacology, Inc. Reprinted by permission of Sage Publications, Inc.[58]

Table 20

OXY-IR Versus OXY-ER: Pharmacokinetics

OXY-IR

Rapid rise in mean plasma concentrations within 1st hour after dosing

High mean degree of fluctuation in plasma concentrations

High incidence of dry mouth

OXY-ER

Oxybutynin released within 3 hours of administration

Plasma concentration fairly constant over 24 hours

High mean relative bioavailability (153% versus 69% for OXY-IR)

Reduced incidence of moderate-to-severe dry mouth (23%)

Few treatment discontinuations

serum concentration provided by the controlled-release formulation also appears to minimize reports of adverse effects that have been associated with the peak-to-trough concentration fluctuations of the original formulation.[59] As a result, the incidence of moderate-to-severe dry mouth is reduced to 23%[60] and causes few treatment discontinuations. As with other anticholinergics, the most common adverse events associated with OXY-ER are dry mouth, constipation, and headache, and appear to be dose-related.[59] In summary, OXY-ER has been shown to be more tolerable than OXY-IR. OXY-ER is available in 5-, 10-, and 15-mg tablets; patients initially receive 5 mg/d, which can then be increased in increments of 5 mg/wk, to a maximum of 30 mg/d.

Tolterodine

Tolterodine is an antimuscarinic agent developed for the management of OAB (Table 21). As with oxybutynin, there are currently two oral formulations of tolterodine—an immediate-release formulation (TOL-IR) (Detrol®) and a once-daily, extended-release (TOL-ER) capsule (Detrol® LA, Pfizer, Inc, New York, NY).

Tolterodine has the same mechanism of action as oxybutynin, but it is metabolized by the CYP2D6 isoform of the hepatic CYP450 system. As a result, there are potential safety concerns for patients with CYP2D6 deficiency and drug interactions (including fluoxetine) associated with the use of tolterodine. The recommended dose of TOL-IR is 4 mg/d (2 mg twice daily) in otherwise healthy patients; the dose can be lowered to 2 mg/d based on individual response and tolerability. The recommended dose for patients with reduced hepatic or renal function is 2 mg/d.[61]

Table 21

Tolterodine: Overview

Similar mechanism of action as oxybutynin

Developed for management of OAB

Potential safety concerns/drug interactions for patients with CYP2D6 deficiency

Two formulations

- Immediate-release (TOL-IR)
  - Dosed 1 mg or 2 mg, 2 times/d
  - High incidence of dry mouth
- Extended-release (TOL-ER)
  - Once-daily dosing 2 mg or 4 mg
  - Improved tolerability over TOL-IR

TOL-IR has been shown to achieve dose-related improvements in frequency of micturition, urgency incontinence episodes, and volume voided per micturition in randomized, double-blind, placebo-controlled, dose-ranging Phase II studies.[62-64] These and other studies consistently demonstrate a 20% reduction in micturition episodes versus placebo, a 40% to 60% reduction in weekly UUI episodes versus placebo, and a 20% increase in mean voided volume. As with other anticholinergics, the most common adverse events associated with TOL-IR are dry mouth, constipation, and headache.[61-66] Side effects appear to be dose-related; the adverse-effect profile of 2 mg/d (33%) is comparable to placebo (39%) but substantially increases at doses of 4 mg bid (57%).

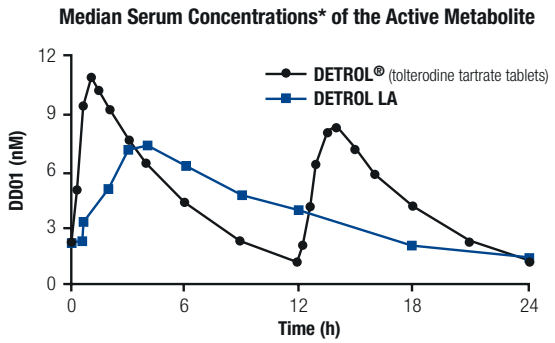
In order to provide a more uniform serum concentration, an extended-release formulation of tolterodine was introduced in 2001 (Figure 8). TOL-ER utilizes a microsphere system similar to that used in over-the-counter sustained-release drug formulations, combining larger beads that slowly dissolve with smaller beads that quickly dissolve. In general, TOL-ER has been shown to be more tolerable than TOL-IR.

Transdermal Oxybutynin

A new method of delivery, the oxybutynin patch, has recently become available for therapeutic use. The oxybutynin transdermal system (OXY TDS) provides an alternative approach in the treatment of OAB. The matrix-type TDS contains 12, 24, or 36 mg of OXY and triacetin (a permeation enhancer) which is dissolved in an acrylic block-copolymer adhesive with surface areas of 13, 26, or 39 cm^2, respectively.[67] The active transdermal system provides a systemic delivery of approximately 3.9 mg of OXY daily.

Figure 8

TOL-ER: Comparative Pharmacokinetics



*From an open-label, randomized, crossover trial in healthy volunteers identified as extensive metabolizers (n=13).

Data collected after 6 days of dosing.

Clinical Trials: Oxybutynin (Immediate-Release and Extended-Release Formulations)

Two randomized, double-blind clinical trials have shown comparably high efficacy between OXY-IR (1 to 4 times/d) and OXY-ER (Table 22).[71,72] OXY-IR decreased weekly UUI episodes by 76%[71] to 88%[72]; OXY-ER reduced UUI episodes by 83%[71] and 84%,[72] and 41% to 50% of patients achieved continence. However, there was a significant difference in the tolerability profiles between the two formulations: OXY-ER was associated with significantly less dry mouth than OXY-IR.[71,72] Similarly, an open-label study found that only 58.6% of patients receiving OXY-ER reported dry mouth upon prompted questioning[59]; this is comparable to the reduced rates observed in the double-blind trials. In general, OXY-ER reduces weekly UUI episodes by 83% to 90% and is more tolerable than OXY-IR.[59,60,71,72]

Table 22

OXY-IR Versus OXY-ER: Clinical Trials

Total No. Patients/ Diagnosis	Treatment	Results
105 patients* Urgency or mixed incontinence	OXY-ER 5-30 mg/d	84% ↓ mean UUI episodes/wk 41% pts achieved continence 68% experienced dry mouth[a] 25% mod-severe dry mouth[b]
	OXY-IR 5 mg qd-qid	88% ↓ mean UUI episodes/wk 40% pts achieved continence 87% experienced dry mouth[a] 46% mod-severe dry mouth[b]
226 patients†	OXY-ER (20 mg/d max)	83% ↓ mean UUI episodes/wk
Urgency/mixed incontinence	OXY-IR (20 mg/d max)	76% ↓ mean UUI episodes/wk
256 patients‡	OXY-ER (5-30 mg/d)	59% experienced dry mouth 23% mod-severe dry mouth

*Anderson RU, et al. *J Urol.* 1999;161(6):1809-1812.[72]
†Versi E, et al. *Obstet Gynecol.* 2000;95(5):718-721.[71]
‡Gleason DM, et al. *Urology.* 1999;54(3):420-423.[59]
[a]P=0.04; [b]P=0.03

Clinical Trials: Tolterodine (Immediate-Release and Extended-Release Formulations)

A Phase III study of more than 1,500 patients compared the efficacy and tolerability of TOL-IR (2 mg bid), TOL-ER (4 mg/d), and placebo.[73] Both tolterodine formulations significantly reduced the mean number of UUI episodes per week (P=0.0001 for TOL-ER and P=0.0005 for TOL-IR), and both formulations significantly decreased the mean micturition frequency (P<0.0079) (Table 23). The TOL-ER formulation was reported as being 18% more effective than the TOL-IR formulation with regard to the median reduction in UUI episodes. (It should be noted that the Food and Drug Administration requires that the "mean" and not the "median" be used in measures of UUI episodes in clinical trials.) An alternative analysis of the study results, utilizing mean versus median percentage reductions, found no significant differences in incontinence episodes from baseline between the two tolterodine formulations.[74] Dry mouth (of any severity) was reported in 23% of patients with TOL-ER, 30% with TOL-IR, and 8% with placebo. TOL-ER was superior to TOL-IR in terms of tolerability.[73]

Table 23

TOL-ER Versus TOL-IR Study

Overview

Phase III study*
>1,500 patients
TOL-ER (4 mg qd) versus TOL-IR (2 mg bid)

Results: TOL-ER Versus TOL-IR

Both TOL-ER (P=0.0001) and TOL-IR (P=0.0005) significantly reduced mean number of UUI episodes/wk versus placebo
Both: significant decrease in mean micturition frequency (P<0.0079)
TOL-ER: significantly reduced rate of dry mouth versus TOL-IR (P<0.02)
Significant difference in median reduction of UUI episodes versus TOL-IR (P<0.05)
No significant difference in mean reduction of UUI episodes†

*Van Kerrebroeck P, et al. *Urology.* 2001;57(3):414-421.[73]
†Cannon TW, Chancellor MB. *Clin Obstet Gynecol.* 2002;45(1):205-217.[74]

Clinical Studies Comparing Oxybutynin Versus Tolterodine

There have been numerous studies comparing OXY-IR with TOL-IR, as well as studies comparing the immediate-release formulation of one agent versus the extended-release formulation of the other (Table 24). However, until recently no direct clinical trials compared the extended-release formulations (OXY-ER versus TOL-ER) on measures of reduction of urgency incontinence, reduction in micturition frequency, and increase in voiding volume.

A comparative trial found that OXY-IR (5 mg tid) reduced UUI episodes by 71% versus a 47% reduction associated with TOL-IR (2 mg bid) and a 19% reduction for placebo; both OXY-IR and TOL-IR achieved comparable reductions in urinary frequency (19.5% OXY-IR versus 21% TOL-IR) that were approximately double that of placebo (10.5%).[75] In a double-blind, multicenter trial, TOL-IR (2 mg bid) was comparable to OXY-IR (5 mg tid) on measures of efficacy.[65]

The Overactive Bladder: Judging Effective Control and Treatment (OBJECT) prospective, randomized, double-blind, parallel-group, multicenter trial compared OXY-ER with TOL-IR and found that after 12 weeks of treatment, OXY-ER 10 mg once daily was statistically superior on all efficacy parameters (weekly urgency incontinence episodes [P=0.03], end-of-study total incontinence episodes [P=0.02], and micturition frequency episodes [P=0.02]) when compared with TOL-IR (2 mg bid).[76] In addition, rates of dry mouth were generally comparable between the two agents (28.1% OXY-ER versus 33.2% TOL-IR) (Table 25).[76]

Table 24

Tolterodine Versus Oxybutynin Studies

Treatment	Results	
OXY-IR (5 mg tid)*	71% ↓ UUI	19.5% ↓ Urinary frequency
TOL-IR (2 mg bid)	47% ↓ UUI	21.0% ↓ Urinary frequency
Placebo	19% ↓ UUI	10.5% ↓ Urinary frequency
OXY-ER (10 mg qd)†	OXY-ER: superior on weekly urgency incontinence (P=0.03)	
TOL-IR (2 mg bid)	OXY-ER: superior on total/mixed incontinence (P=0.022) OXY-ER: superior on micturition frequency (P=0.022) Comparable rates of dry mouth (28.1% OXY-ER versus 33.2% TOL-IR)	
OXY-IR (2.5-5 mg tid)‡	OXY-IR: 50% greater reduction in urinary incontinence	
TOL-IR (1-2 mg tid)	OXY-IR: more significant increase in mean voided volume TOL-IR: significantly less dry mouth TOL-IR: significantly fewer treatment discontinuations	

*Abrams P, et al. *BJU Int.* 1998;81(6):801-810.[75]
†Appell RA, et al. *Mayo Clin Proc.* 2001;76:358-363.[76]
‡Harvey MA, et al. *Am J Obstet Gynecol.* 2001;185(1):56-61.[77]

This regimen offers twice-weekly dosing to either the abdomen, hip, or buttock. Rotation of the application site (at least 1 week between applications to the same site) is recommended in order to avoid skin reactions such as erythema or pruritus.[68] Transdermal delivery of oxybutynin appears comparable in efficacy to oral administration, but with a lower incidence of side effects.[68] OXY TDS avoids extensive first-pass metabolism, resulting in a significant reduction in circulating levels of the primary active metabolite, *N-desethyloxybutynin* (DEO). DEO is associated with a high incidence of anticholinergic side effects that have been observed following oral administration of OXY.[67] As a result, there is less incidence of dry mouth with OXY TDS than with the oral formulation.[68] OXY TDS provides steady-state and continuous delivery per application, resulting in the reduction of peak-to-trough fluctuations in plasma concentrations that typically occur with oral administration.[69] The two most common application-site adverse events observed were pruritus (16.8%) and erythema (5.6%); therefore, it is important for patients to rotate this regimen accordingly as previously discussed.[70]

Future Research Priorities

Priorities for future research include a variety of improved formulations of anticholinergics, including bladder-specific anticholinergics; selective M3 receptor antagonists; serotoninergic antagonists; dual-acting anticholinergic/calcium channel blockers; neuronal desensitizing agents; and potassium channel openers. In addition, alternative delivery systems for oxybutynin are under investigation.

Surgical Options

Surgical management traditionally has been reserved as a last resort for OAB management. However, neuromodulation, a minimally invasive procedure, has increased the demographic of patients eligible for intervention at a much less severe stage of OAB. Previously, ideal candidates for surgery included patients with long-standing decreased bladder capacities resulting from DO that produced high-grade incontinence and who did not respond to any previous conservative medical or behavioral management strategies and whose QOL has been severely affected. Candidates must be willing to undergo lifelong medical follow-up. The goal of neuromodulation and augmentation is to increase the bladder's storage capacity and to decrease the detrusor activity producing incontinence. The majority of surgical candidates for augmentation are patients with neurogenic bladder secondary to spinal cord injury or other neurologic disease. Urinary diversion is reserved for end stage bladder disease.

Special Populations

PCPs can generally manage the diagnosis and treatment of OAB in women and, frequently, in pediatric patients. However, because of the challenges associated with the diagnosis and/or management of OAB in other populations—particularly in men and in the infirm elderly—referral to a specialist may be necessary. Nevertheless, initial suspicion of OAB in these populations is often the responsibility of the PCP.

Clinical Trials Comparing Oxybutynin-ER Versus Tolterodine-ER

Finally, two trials comparing the extended-release formulations of tolterodine and oxybutynin have recently been conducted. The first, the Antimuscarinic Clinical Effectiveness Trial (ACET), compared TOL-ER (2 mg and 4 mg qd) to OXY-ER (5 mg and 10 mg qd) in a combination of independent trials that were prospective, nonblinded, open-label, nonrandomized trials. The trial measured primary study outcomes by using questionnaires about patient and physician subjective perceptions regarding drug treatment at baseline and at week 8. A total of 1,289 patients were enrolled in the study with 669 receiving TOL-ER and 620 receiving OXY-ER. Efficacy was measured by patient perception of bladder condition. The patient perception of efficacy was significantly more effective, reported as 70% for TOL-ER (4 mg qd) compared to 60% for both TOL-ER (2 mg qd) and OXY-ER (10 mg qd) (Table 25).[78]

The Overactive bladder: Performance of Extended Release Agents (OPERA) trial, a prospective, randomized, double-blind, parallel-group study, compared the efficacy of extended-release formulations of oxybutynin and tolterodine, using objective measures for the study outcomes. Of the 790 women randomized, 391 received OXY-ER (10 mg qd) and 399 were given TOL-ER (4 mg qd). The study showed that tolerability of OXY-ER and TOL-ER were similar; however, total dry mouth was more common with OXY-ER. Both agents showed comparable reduction in the primary endpoint of weekly UUI episodes; however, OXY-ER was significantly more effective than TOL-ER in reducing micturition frequency (P=0.003) with a higher percentage of patients reaching total dryness with OXY-ER (23.0%) versus TOL-ER (16.8%) (P=0.029) (Table 25).[3]

Table 25

Most Recent Oxybutynin Studies Versus Tolterodine Studies: Summary

Outcome	OBJECT Study N=378	ACET Study N=1289	OPERA Study N=790
Reduction in Incontinence Episodes	OXY-ER S more reduction than TOL-IR	Not stated	NS difference in reduction OXY-ER versus TOL-ER
Reduction in Frequency	OXY-ER S more reduction than TOL-IR 28% greater reduction with OXY-ER	Not stated	OXY-ER S more reduction than TOL-ER
Total Dryness	Not stated	Not stated	OXY-ER 23% S higher versus TOL-ER 17%
Tolerability	NS difference between AC AEs between arms 28% OXY-ER versus 32% TOL-IR with dry mouth No difference in CNS AEs	6% TOL-ER versus 13% OXY-ER withdrew from study S S less AC AEs TOL-ER versus OXY-ER	NS difference between AC AEs (mild, moderate, and severe) between arms except for all degrees of dry mouth. S more for OXY-ER versus TOL-ER No difference in CNS AEs
Study Design	RCT	Open-label, nonblinded, randomized on basis of dosing in arm, subjective measures	RCT
Comments	QOL changes similar between arms	Improvement 70% TOL-ER versus 59% OXY-ER S, based on subjective patient measures Improvement noted for both moderately and severely affected patients	Both drugs noted to have rapid onset of action (by 2 weeks) with further increase to 8 weeks

AC=anticholinergic; AE=adverse event; CNS=central nervous system; NS=not statistically significant; OXY=oxybutynin chloride; QOL=quality of life; RCT=randomized controlled trial; S=statistically significant; TOL=tolterodine tartrate.

Children

OAB is the most common voiding dysfunction in children. It can present as acute daytime frequency syndrome, detrusor instability secondary to detrusor (external) sphincter dyssynergia, or as the Hinman syndrome (Table 26). In addition, some neurogenic conditions, such as spina bifida occulta or a tethered spinal cord, can first manifest with bladder dysfunction.

Table 26

Pediatric OAB

Acute daytime frequency syndrome
Unknown pathophysiology—viral or bacterial
Detrusor instability secondary to detrusor (external) sphincter dyssynergia
Hinman syndrome
Most severe voiding dysfunction in children
Neurogenic bladder in absence of neurologic lesions
Requires aggressive therapy

Bladder emptying in a neonate is the result of a sacral spinal cord reflex; as the child matures, the pontine micturition center assumes control of voiding. Many bladder control problems in children (and possibly adults) are the result of not initially learning the correct way to void. The majority of children attain voluntary control of bladder fullness between 2 and 4 years of age. While OAB can manifest at any age thereafter, it is most commonly observed in children aged 5 to 7 years and is most prevalent in girls. Clinical evaluation of a child must first determine whether it is the child or the parent who is concerned with the OAB; whether the OAB is medically or socially significant; and whether the pediatric urinary incontinence is nocturnal, diurnal, or both. Otherwise, the evaluation of pediatric OAB is, in many ways, similar to that of adult OAB. However, unlike in an adult, evaluation of pediatric OAB also should include a mental health assessment to rule out any psychologic basis to the condition. The clinician should look for possible abuse, significant stress from home or school, or any recent significant disruption in the child's life, such as divorce or death in the family.

Pediatricians and PCPs are frequently reluctant to manage OAB in children because it can be very time-consuming. Nevertheless, as with diagnosis, treatment for pediatric OAB is very similar in nature to that for adult OAB and employs a combination of behavioral interventions and pharmacologic therapies. Reward- or goal-oriented timed voiding, in which children are instructed to void every 3 hours, is an extremely effective intervention in children. Children, unlike adults, are easy to retrain, particularly when the change is goal- or prize-oriented. Biofeedback training for DO also has been shown to be effective,[79] but it is usually reserved for those children who cannot learn timed voiding by other means.

Children who do not respond to behavioral interventions may require an anticholinergic agent. OXY-IR is indicated for use in pediatric patients 6 years of age and older and is available in tablet form and in liquid suspension for children who are not yet capable of swallowing pills. OXY-ER is now indicated for the treatment of patients 6 years of age and older with neurogenic conditions such as spina bifida.[60] Tolterodine is not indicated for use in children; however, recent studies have shown tolterodine 1 mg twice daily for 2 weeks to be safe and effective in children aged 5 to 10 years.[80] Recent research found OXY-ER to be comparable in efficacy to TOL-ER in the management of pediatric diurnal urinary incontinence, and more effective than either TOL-IR or TOL-ER in the management of daytime urinary incontinence and frequency.[81]

Finally, for children who require aggressive therapy, urethral dilatation, intermittent catheterization, and augmentation may be indicated.

Elderly

OAB is an age-associated disease, and elderly persons have the highest prevalence of OAB. However, age is not a causative factor and OAB is not an inevitable consequence of aging. It is not necessarily related to cognitive function; incontinence and OAB may, in fact, be the result of impairments in mobility or manual dexterity or changes to the lower urinary tract. OAB and urinary incontinence are, however, major causes of institutionalization of the elderly.

There are important differences in the presentation, diagnosis, and management of OAB among elderly patients based upon their health and level of independence. As a group, the elderly have a greater likelihood of comorbid conditions that could be associated with incontinence or OAB (Table 27), and they are therefore more likely to utilize medications that can mimic OAB, including sedatives, diuretics, anticholinergics, and antihypertensives (Table 28). Differential diagnosis is comparable to that of their younger cohorts, albeit with greater emphasis on transient and functional causes. It should be remembered, however, that OAB is not always associated with prostate disease in elderly men.

The elderly may be the least likely population to freely raise bladder health concerns with a clinician during a general examination. As a result, it is incumbent upon the PCP to routinely ask questions to assess bladder symptomatology and impact on QOL. These data may be elicited from caregivers for patients living in long-term care facilities. PCPs should always be alert to the possibility of bladder or prostate cancer, previously occult spinal cord injuries or

Table 27

Risk Factors of OAB in the Elderly

Depression	Constipation
Stroke	Obesity
Congestive heart failure	Prostate disease
Chronic obstructive pulmonary disease	Cough
Impaired mobility	Poor activities of daily living
Concomitant medications	

Table 28

Medications That Mimic OAB

Sedative hypnotics (including alcohol)

Diuretics (R_X and caffeine)

Anticholinergics

- Tricyclic antidepressants
- Antipsychotic agents
- Antihistamines
- Narcotics

Antihypertensives

- α-Blockers
- Calcium channel blockers
- ACE inhibitors

Drugs causing edema

- NSAIDs
- Gabapentin
- Nifedipine
- Rosiglitazone

tumors, and urinary retention in elderly patients who present with OAB. As with pediatric patients, geriatric patients with suspected OAB often require a more comprehensive physical examination that includes neurologic, rectal, and pelvic assessment, as well as a complete medication review. Urodynamic testing is reserved only for patients who have failed pharmacologic treatment or are surgical candidates.

OAB in the elderly patient is treated similarly to OAB in younger patients by utilizing a multifactorial approach that incorporates behavioral interventions and pharmacologic treatments. Behavioral interventions may not be as effective among elderly patients with dementia or reduced cognitive functioning, or among patients in long-term care facilities. Pharmacotherapy includes the anticholinergic agents oxybutynin and tolterodine. Clinicians should be aware of age-related changes in volume of distribution and renal/hepatic function in this population, which could increase the likelihood of adverse effects at lower doses.[82] Finally, recommendations for lifestyle changes include weight reduction for the massively obese, smoking cessation, and reducing caffeine intake.

Men

Nearly one in three men over the age of 50 report lower urinary tract symptoms (LUTS), and more than 8% of those require surgery.[83] Bladder symptoms appear to be more prevalent among men than women over age 75,[17] predominantly related to bladder outlet obstruction (BOO) or prostatitis. PCPs rarely have the tools/technology necessary for the diagnosis of bladder concerns in men; as such, males who present with bladder symptomatology are traditionally referred to a specialist for diagnosis, but they can often be managed by a PCP.

Until recently, LUTS in men were presumed to be primarily the result of intravesical (prostatic) obstruction or secondary effects of obstruction on the bladder. However, research now suggests that the bladder also may be a primary source of LUTS in men. Evaluation of bladder symptoms should attempt to distinguish between BOO and OAB unrelated to obstruction (Table 29). In contrast to the urgency, frequency, and possible urgency incontinence associated with OAB, BOO may also manifest as obstructed voiding, straining, hesitancy, and slow stream. The diagnostic process emphasizes evaluating BOO, particularly with regard to prostate disease, prostate enlargement, bladder neck obstruction, urethral stricture disease, and benign prostatic hyperplasia (BPH). BPH affects at least one in two men over the age of 50,[84] and it can lead to benign prostatic enlargement and ultimately to BOO.[85] Recent research suggests that BOO influences the detrusor muscle and may eventually cause it to become dysfunctional.

Noninvasive diagnostic tests for LUTS in men include a physical examination, symptom questionnaires, a voiding log, flow rate assessment, and ultrasound determination of residual urine. A physical exam focuses on prostate enlargement; however, research suggests that physicians grossly underestimate the prostate size when measured by digital rectal examination.[86] An enlarged prostate generally correlates with the need for surgery and can determine which patients are most likely to respond to 5-α reductase inhibitors such as finasteride.[87] It also may correlate with the severity of LUTS.[88] Questionnaires, including the American Urological Association (AUA) symptom index and the International Prostate Symptom Score (I-PSS) questionnaires, can help assess which patients might require immediate treatment for bladder dysfunction and which might be appropriate for "watchful waiting"; however, they cannot differentiate among the bladder disorders.[89] A voiding diary determines micturition frequency and voided volumes but cannot determine the likelihood of DO.[90] Finally, significantly reduced flow rates are predictive of BOO,[91] but they do not rule out impaired detrusor contractility. Furthermore, flow rates have been shown to correlate with age, voided volume, and prostate size.[92] In summary, noninvasive diagnostic testing is inconclusive in determining whether the bladder symptoms are BOO or DO; invasive diagnostic assessments are necessary.

Surgery may be indicated for patients diagnosed with BOO who do not respond to medical therapy. Interestingly, approximately 70% of patients with OAB will report symptom relief following transurethral resection of the prostate (TURP) for BOO, possibly resulting from an

Table 29

Etiology of LUTS in Men

Disorders of Voiding: BOO	**Inflammatory/Infectious Disorders**
BPH/benign prostatic enlargement	Interstitial cystitis
Bladder neck obstruction	Prostatitis
Urethral stricture	PFD
Disorders of Filling	**Other**
OAB	Carcinoma in situ
Neurogenic	Bladder stones

independent heat effect of TURP on periprostatic nerves or receptor antagonism at peripheral ganglia or more central pathways.[93-95] At least 50% of patients with BOO have DO; the greater the severity of BOO, the greater the incidence of concomitant DO.[96] For patients diagnosed with concomitant BOO plus OAB, most clinicians choose to treat BOO first.[97]

Related Diseases: Impact on OAB

Among the numerous urogenital diseases or conditions that manifest with symptomatology similar to that of OAB are fecal incontinence, pelvic support disorders—particularly pelvic organ prolapse (POP) and CPPSs (encompassing IC, vulvar vestibulitis/vulvodynia, and nonbacterial prostatitis [NBP]) (Table 30). All of these conditions can present clinically with urinary urgency and frequency, with or without urgency incontinence, and there is preliminary evidence suggesting associations among the various conditions. As a result, patients presenting with any one of these conditions should concomitantly be evaluated for the presence of the others.

Table 30

OAB: Related Conditions

- Fecal incontinence
- Pelvic support disorders/pelvic organ prolapse
- Chronic pelvic pain syndromes
  - Interstitial cystitis
  - Vulvar vestibulitis syndrome
  - Nonbacterial prostatitis

Fecal Incontinence

Fecal (or anal) incontinence is another medical condition that can severely and negatively affect QOL (Table 31). It is strongly associated with depression, anxiety, and increasing disability,[98] and it has been associated with reduced social activities[99] and interference with routine daily activities.[100] To date, there have been no definitive studies on this condition. Prevalence rates are difficult to ascertain: patients are often embarrassed to discuss the condition with their clinician and do not believe there are effective therapies.[98] Consequently, estimates of the prevalence of fecal incontinence range from 1% to 11% of men and 4% to 15% of women over 50,[98,101] with an estimated 5% of adult men and women unable to control solid stools.[99] There appears to be a small increased risk with age.[98]

There is a high incidence of comorbidity between urinary incontinence, POP, and fecal incontinence. It has been estimated that nearly 6% of men and 9% of women in the general population have combined urinary and fecal incontinence.[101] The prevalence of urinary incontinence among patients diagnosed with fecal incontinence is high, with estimates ranging from 51% of men and 60% of women in one study[101] to nearly 70% of men and women in another.[98] However, the relative odds of fecal incontinence in patients with urinary incontinence are lower than the relative odds of urinary incontinence among patients with fecal incontinence.[101,102] Additional risk factors include greater body mass index and delivery of large birth-weight infants.[102]

Pelvic Support Disorders and Pelvic Organ Prolapse

Pelvic support disorders, encompassing urinary incontinence, anal incontinence, and POP, account for nearly 400,000 surgical procedures annually in the United States.[103] Pelvic support disorders cause numerous urinary, fecal, and sexual disorders, and they can have a significant impact on a patient's QOL. Despite the absence of reliable epidemiologic studies, recent research found that the overwhelming majority of women attending four outpatient gynecology clinics had mild to moderate pelvic support defects based upon the Pelvic Organ Prolapse Quantification (POP-Q) System.[104] The risk of POP was shown to increase with increasing age, increasing gravidity/parity, increasing number of vaginal births, hysterectomy, or a history of POP surgeries, hypertension, and postmenopausal status.[104] BOO also is associated with a higher-grade prolapse.[105] In addition, prolapse of the pelvic organs, including the bladder, rectum, and/or uterus, has been associated with incontinence[105] as well as with reduced sexual activity and sexual functioning.[106] Severity of prolapse appears to be indicative of severity of OAB symptomatology and detrusor instability.[105] Finally, while there do not appear to be any racial differences regarding the prevalence or severity of pelvic floor prolapse in African-American and Caucasian American women,[26,107] there does appear to be a strong association between stress incontinence, pelvic organ prolapse, and white race.[26]

Chronic Pelvic Pain Syndromes

CPPSs encompass a variety of conditions, the most common of which are IC and NBP/prostatodynia.

Interstitial Cystitis

Patients with IC present with urgency, frequency, and pelvic pain of at least 6 months' duration without a diagnosable etiology (Table 32).[108] Chronic prostatitis is the most common urologic diagnosis in men under age 50[109]; however, research now suggests that many men with IC are in fact misdiagnosed with chronic NBP.[110] Patients with IC are frequently misdiagnosed with UTIs or OAB due to similarities in the clinical presentations of these syndromes and confusion regarding the diagnostic definition of IC.[108]

As with other chronic pain syndromes, IC can have a devastating impact on QOL. In fact, patients with progressive IC are significantly more likely to report thoughts of suicide and to be treated for emotional problems[111] than the general population, and the physical and psychological impact of NBP has been shown to be at least comparable to that of patients suffering myocardial infarction, angina, or Crohn's disease.[112]

Table 31

Fecal Incontinence

- 1% to 15% of population over age 50
- More prevalent in women than men
- Negative impact on QOL
- Patients reluctant to seek help
- Documented association with urinary incontinence

Recently, important advances have been made in the diagnosis and treatment of IC. While cystoscopy with hydrodistention under anesthesia remains of great utility in confirming a diagnosis of IC, many studies demonstrated that cystoscopy may be limited to diagnosis of severe disease stage. The outpatient potassium sensitivity test can be used to identify patients who have a bladder component (such as IC) to their chronic pelvic pain. Similarly, high scores (≥15) on the Pelvic Pain Urgency and Frequency Patient Symptom Scale appear to be suggestive of a diagnosis of IC.[113] The first effective oral treatment option, pentosan polysulfate sodium, has recently been introduced, and it may be preferable to traditional intravesical therapies with dimethyl sulfoxide or heparin. IC should be suspected in patients with recurrent UTI symptoms who fail to respond to antibiotics, patients with OAB who fail to respond to anticholinergics, and patients who present with chronic pelvic pain of unknown etiology, including patients with refractory endometriosis or prostatitis.

Nonbacterial Prostatitis

According to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) classifications of prostatitis,[114] category III prostatitis encompasses the male chronic pelvic pain syndromes (MCPPSs), including nonbacterial/noninflammatory prostatitis (MCPPS category IIIB). NBP is characterized by pelvic pain, perineal pain, testicular pain, penile pain, and/or pain with intercourse or ejaculation. A differential diagnosis for NBP is IC, as men diagnosed with IC frequently experience urinary urgency and frequency, pelvic pain, and pain with intercourse. In fact, evidence suggests that many men with IC are misdiagnosed with chronic NBP or BPH.[110] Both conditions are characterized by a negative urine culture and some (but limited) abnormalities on cystoscopy. There are, as yet, no objective tests or lab analyses to definitively diagnose CPPSs; instead, diagnosis depends upon symptomatic presentation of pelvic pain, irritative and obstructive voiding symptoms, and sexual dysfunction. The NIH Chronic Prostatitis Collaborative Research Network has developed a Chronic Prostatitis Symptom Index (CPSI) that provides a reliable measure to identify men with chronic NBP.[114] Finally, clinicians must rule out prostate enlargement or BPH before diagnosing CPPS or male presentation of IC.

Table 32

Interstitial Cystitis

Urinary urgency + frequency + chronic pelvic pain (>6 months)
Significant impact on QOL
Diagnosis
Cystoscopy with hydrodistention (general anesthesia)
Potassium sensitivity test
Pelvic Pain Urgency and Frequency (PUF) Patient Symptom Scale
Management
Oral pentosan polysulfate sodium
Intravesical dimethyl sulfoxide

Role of the Healthcare Professional in Identifying and Managing OAB

PCPs—whether family practitioners, internists, geriatricians, pediatricians, gynecologists, or "physician extenders" (nonphysician clinicians such as nurse practitioners and physician assistants)—are generally the first point of contact in the healthcare system. As a group, primary care professionals are responsible for identifying bladder symptomatology as well as diagnosing and treating most common bladder disorders. This involves screening for bladder health, counseling about the disease, identifying treatment goals, and providing the appropriate nonpharmacologic, nutritional, and pharmacologic interventions. PCPs also are responsible for identifying which patients require additional diagnostic testing and for coordinating care with specialists.

Oftentimes, physician extenders have more time and availability than physicians to provide the necessary education and counseling associated with the management of OAB. Their more "holistic" approach to medicine facilitates health promotion and disease prevention, and it may enable patients to ask more questions as well as raise health-related concerns that are less likely to be addressed during the short-duration, problem-oriented office visits with physicians. Physician extenders, and particularly nurse practitioners, often are perceived as being more approachable and more willing to listen than physicians.[115] Female patients are more likely to seek out female versus male health workers to discuss specific "women's health issues."[116] As a result, physician extenders are an important addition to a primary care practice and can be an integral component in the diagnosis and management of OAB.

Conclusions

OAB should no longer be a "taboo" topic for either patients or PCPs. Bladder control problems affect a significant number of people, the majority of whom remain untreated or undertreated. Today's PCPs face several challenges: (1) integrating bladder health questions into their general medical assessments in order to identify patients with OAB symptoms; (2) utilizing a diagnostic approach aimed at excluding conditions with common presenting symptoms; (3) instituting a combination of behavioral, physical, and pharmacologic therapies; and (4) maintaining communication with the patient to maximize therapy. For the majority of women, the diagnosis and management of OAB is well within the clinical parameters of PCPs. While advanced diagnostic testing by a specialist is often necessary for pediatric, geriatric, and male patients, PCPs can generally coordinate and assume responsibility for the ongoing management of these populations. The integration of physician extenders into a primary care practice allows for patient counseling, support, and education, and it may enhance the diagnostic and therapeutic process for all patients with OAB.

A variety of related conditions and diseases, including disorders of intake and output or conditions that affect fluid balance; inflammatory conditions such as chronic cystitis

and IC; and underlying benign or malignant urologic, gynecologic, or colorectal disorders may present with symptomatology similar to that of OAB. In female patients, atrophic vaginitis and other inflammatory conditions may complicate diagnosis. In male patients, benign or malignant prostate disease that affects bladder emptying and filling may complicate therapy. Special considerations in pediatric, geriatric, and neurologic populations have been reviewed. These conditions also can coexist with OAB; as a result, patients with any of these conditions should be evaluated for the presence of the others.

Current management strategies have demonstrated that a multimodal approach of behavioral, physical, and pharmacologic therapy works better than individual approaches. Advances in drug delivery utilizing extended release and patch technologies have improved the efficacy:tolerability ratio of both oxybutynin and tolterodine. Comparative studies of the agents and their formulations are now available.

Future advances will target more uro-specific agents, further improve drug delivery, and direct therapies to the afferent system, alone or in combination with agents that currently affect efferent transmission. Surgical therapies have traditionally been reserved as a last resort for patients with severe symptoms. Although the conference focused on nonsurgical approaches, advances in neuromodulation and sacral nerve stimulation suggest that stimulation of the sacral nerves provides a viable alternative to more invasive intra-abdominal surgical procedures designed to increase bladder capacity.

The experts from this roundtable meeting clearly indicated that with a basic understanding of diagnostic methods and with currently available therapies, physicians can effectively treat OAB in the primary care setting. In particular, there is a need to focus on evaluating for urinary incontinence, as women with OAB wet are more likely to be bothered by their symptoms and therefore more likely to seek and receive treatment. With the physician and patient goal of treating to total dryness, women with UUI may benefit most from current therapeutic approaches and future treatment advancements.

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CME Quiz

1. According to the Standardisation Sub-committee of the International Continence Society, OAB is characterized by which cluster of symptoms?
   a. Urinary urgency, urinary frequency, chronic pelvic pain
   b. Urinary urgency with significant nocturia
   c. Urinary urgency, urge incontinence, urinary frequency
   d. Urinary frequency, pelvic pain
2. Population studies have demonstrated that nearly half of all patients with OAB are aged:
   a. 18 to 35 years
   b. 40 to 64 years
   c. 50 to 75 years
   d. ≥65 years
3. In addition to a physical examination and medical history, initial diagnosis of OAB by a PCP should always include:
   a. Urinalysis (with or without culture)
   b. Cystometry/cystometrography
   c. Postvoiding residual (PVR) test
   d. All of the above
4. OAB is considered a:
   a. Failure to store/bladder outlet problem
   b. Failure to store/bladder problem
   c. Failure to empty/bladder problem
   d. Failure to empty/bladder outlet problem
5. Bladder training involves:
   a. Biofeedback
   b. Timed voiding with increasing intervals between voids
   c. Pelvic floor muscle exercises
   d. All of the above
6. In comparison to the original formulation, the extended-release formulation of oxybutynin:
   a. Allows for once-daily dosing
   b. Affords a gradual increase in mean plasma concentration over 6 hours
   c. Significantly reduces the incidence of dry mouth
   d. All of the above
   e. None of the above
7. Which of the following is true regarding TOL-ER?
   a. It utilizes osmotic release technology.
   b. It was developed specifically for the management of OAB.
   c. It is metabolized by the CYP2D6 isoform of the hepatic CYP450 system.
   d. All of the above
   e. B and C
8. Which of the following statements is most accurate?
   a. OXY-ER is more tolerable and more effective than OXY-IR.
   b. OXY-ER is comparably effective and more tolerable than OXY-IR.
   c. TOL-ER is more effective and more tolerable than TOL-IR.
   d. TOL-ER is more effective and comparably tolerable to TOL-IR.
9. Comparative studies suggest that:
   a. OXY-ER is both more effective and more tolerable than TOL-ER
   b. TOL-ER is both more effective and more tolerable than OXY-ER
   c. OXY-ER is more effective but slightly less tolerable than TOL-ER
   d. TOL-ER is more effective but slightly less tolerable than OXY-ER
10. Pediatric OAB is most commonly observed in:
    a. Girls aged 2 to 4
    b. Girls aged 5 to 7
    c. Boys aged 2 to 4
    d. Boys aged 5 to 7
11. Differential diagnosis for OAB among elderly patients should include:
    a. Dementia
    b. Comorbidities
    c. Medications that can cause incontinence
    d. All of the above
12. In men, bladder outlet obstruction (BOO) manifests as:
    a. Urinary urgency, frequency, and chronic pain
    b. Obstructed voiding and urinary urgency
    c. Obstructed voiding, hesitancy, and slow stream
    d. Urinary urgency and leakage with exertion
13. Which of the following chronic pelvic pain syndromes presents with urinary urgency, urinary frequency, and chronic pelvic pain?
    a. Pelvic organ prolapse
    b. Interstitial cystitis
    c. Vulvar vestibulitis syndrome
    d. Fecal incontinence

Answers: 1.___ 2.___ 3.___ 4.___ 5.___ 6.___ 7.___ 8.___ 9.___ 10.___ 11.___ 12.___ 13.___

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